

AMENDMENTS TO THE SPECIFICATION

Please amend the paragraph beginning on page 7, line 21 as follows:

The invention also provide RANTES variants obtainable by the methods of the invention and having the general formula *S#SSQ&&-RANTES(10-68) (SEQ ID NO: 24), in which:

- * is L or an aromatic residue,
- # is L, M or V,
- & is S, P, T or A.

Please amend the paragraph beginning on page 8, line 3 as follows:

In a preferred embodiment, the RANTES variants have a N-terminal amino-acid sequence selected among the following sequences (SEQ ID NOS: 1 -18):

LSPVSSQSSA (P₁), FSPLSSQSSA (P₂), LSPMSSQSPA,
WSPLSSQSPA, WSPLSSQSSP, LSPQSSLSSS, ASSGSSQSTS, ISAGSSQSTS,
RSPMSSQSSP, YSPSSSLAPA, MSPLSSQASA, ASPMSSQSSS, QSPLSSQAST,
QSPLSSTASS, LSPLSSQSAA, GSSSSSQTPA, YSPLSSQSSP, FSSVSSQSSS,

or, among the following sequences:

VSTLSSPAST (SEQ ID NO: 30), ASSFSSRAPP (SEQ ID NO: 31),
QSSASSSSSA (SEQ ID NO: 32), QSPGSSWSAA (SEQ ID NO: 33), QSPSSWSSS
(SEQ ID NO: 34), QSPLSSFTSS (SEQ ID NO: 35), ASPQSSLPAA (SEQ ID NO:
36), LSPVSSQSSA (SEQ ID NO: 1), LSPQSSLSSS (SEQ ID NO: 6).

Please amend the paragraph beginning on page 9, line 26 as follows:

In a more preferred embodiment, they have the formula FSPLSSQSSA (SEQ ID NO: 2)-RANTES(10-68) (P2), or LSPVSSQSSA (SEQ ID NO: 1)-RANTES (10-68) (P1).

Please amend the paragraph beginning on page 9, line 29 as follows:

In another preferred embodiment, clones selected by binding to CHO-CCR5, without internalization, have their N-terminal amino-acid sequence selected among the following sequences:

VSTLSSPAST (SEQ ID NO: 30), ASSFSSRAP (SEQ ID NO: 31), QSSASSSSA (SEQ ID NO: 32), QSPGSSWSAA (SEQ ID NO: 33), QSPSSWSSS (SEQ ID NO: 34), QSPLSSFTSS (SEQ ID NO: 35), LSPQSSLSS (SEQ ID NO: 36), ASPQSSLPAA (SEQ ID NO: 36), LSPVSSQSSA (SEQ ID NO: 1).

Please amend the paragraph beginning on page 17, line 22 as follows:

The DNA sequence encoding tag HA 1.1 (YPYDVPDYA) (SEQ ID NO: 19) was cloned into the phagemid pHEN1 (26), kindly provided by G. Winter, between restriction sites *Nco*I and *Not*I. The DNA sequence coding for human RANTES, amplified from cDNA prepared from activated human PBMCs, was used as the scaffold for library construction. PCR mutagenesis of the 5' portion of the gene was performed using a specific downstream primer 5'-TGG GGC CCC TCT AGA CAT CTC CAA AGA GTT GAT GTA CTC (SEQ ID NO: 20) (the recognition sites for *Psp*OMI and *Xba*I - in that order - are underlined) and a degenerate upstream primer 5'-CTC GCG GCC CAG CCG GCC ATG GCC NNK TCC NCA NNK TCC TCG NNK NCC NCA NCC TGC TGC TTT GCC TAC ATT GCG CGG CCG CTG CCC CGT GCC CAC ATC (SEQ ID NO: 21) (underlined:

recognition sites for *NcoI* and *NotI*). The purified PCR product was cut with *NcoI* and *PspOMI* and inserted into pHEN1, previously linearized using *NcoI* and *NotI*. The ligated DNA was electroporated into *Escherichia coli* TG1. Cells were grown for 1 hour in SOC medium at 37°C, and then plated on LB-agar dishes containing 100 µg/ml ampicillin and 1% (w/v) glucose. Certain colonies were screened by PCR before selection and their DNA insert was sequenced using an automatic sequencer ABI 377 (Perkin Elmer, USA). In this way the complexity of the expressed library was determined to be at least 5×10^6 , thus exceeding its theoretical diversity (2×10^6 : the number of possible combinations of amino acids). Phage stocks were prepared essentially as in (26).

Please amend the paragraph beginning on page 21, line 1 as follows:

The interaction between chemokines and their cognate receptors is influenced by cell type-dependent variations in both the quantity and type of cellular components, for example cell surface proteoglycan (31) and intracellular proteins involved in receptor endocytosis (32). The inventors therefore chose to use two different cellular backgrounds, Human Embryonic Kidney (HEK) and Chinese Hamster Ovary (CHO), for our biopanning strategy. Three independent biopanning experiments were carried out, each of which features three rounds of selection (and amplification). In two cases, a single cell background was used in each of three rounds (HEK-CCR5; CHO-CCR5), while a third strategy involved alternating the cell background between rounds (HEK-CCR5 & CHO-CCR5). Comparison of the selected sequences enabled us to define a consensus sequence, LSP#SSQSSA (SEQ ID NO: 29).

Please amend the table beginning on page 22, line 1 as follows:

N-terminal sequence
of selected clones

Total

<u>(SEQ ID NO:)</u>		Cell lines used for selection			Total
		HEK-CCR5	CHO-CCR5	HEK-CCR5 & CHO- CCR5	
LSPVSSQSSA (1)	(P1)	6		4	10
FSPLSSQSSA (2)	(P2)		6		6
LSPMSSQSPA (3)		6	1	4	11
WSPLSSQSPA (4)		1		1	2
WSPLSSQSSP (5)		2			2
LSPQSSLSSS (6)		1			1
ASSGSSQSTS (7)		1			1
ISAGSSELAA (22)		1			1
RSPMSSQSSP (9)		1			1
YSPSSSLAPA (10)		1			1
MSPLSSQASA (11)			1		1
ASPLSSQSSS (23)			1		1
QSPLSSQAST (13)			1		1
QSPLSSTASS (14)			1		1
LSPLSSQSAA (15)			1		1
GSSSSSQTPA (16)				1	1
YSPPLSSQSSP (17)				1	1
FSSVSSQSSS (18)				1	1
<u>Total</u>		20	12	12	44

LSP*SSQSSA (25)	Consensus (biopanning on CCR5 ⁺ cells)
RSPPSRRAS (26)	Consensus (panning on 1D2 antibody)
SPYSSDTTP (27)	Wild-type RANTES
XS#XSX### (28)	RANTES library

Please amend the table beginning on page 23, line 5 as follows:

Table 2 hereinafter displays the sequences of clones selected by binding to CHO-CCR5 cells. Selection was based toward Phage clones able to bind cell surface without subsequent internalization.

N-terminal sequences of selected clones	Number of clones
<u>VSTLSSPAST</u> (SEQ ID NO: 30)	1
<u>ASSFSSRAPP</u> (SEQ ID NO: 31)	1
<u>QSSASSSSSA</u> (SEQ ID NO: 32)	1
<u>QSPGSSWSAA</u> (SEQ ID NO: 33)	1
<u>QSPPSWSSS</u> (SEQ ID NO: 34)	2
<u>QSPLSSFTSS</u> (SEQ ID NO: 35)	1
<u>LSPVSSQSSA</u> (SEQ ID NO: 1)	1
<u>LSPQSSLSSS</u> (SEQ ID NO: 6)	5
<u>ASPQSSLPAA</u> (SEQ ID NO: 36)	4
<u>QSPQSSØSSA CONSENSUS 1</u> (SEQ ID NO: 37)	Ø = aromatic residue
<u>LSPQSSLSSX CONSENSUS 2</u> (SEQ ID NO : 38)	
<u>XS#XSSX### library*</u> (SEQ ID NO: 28)	
Key to symbols: Ø=Aromatic residue, # = A, P, S or T.	

IN THE SEQUENCE LISTING

Please replace the Sequence Listing of record with the Substitute Sequence Listing enclosed herewith.